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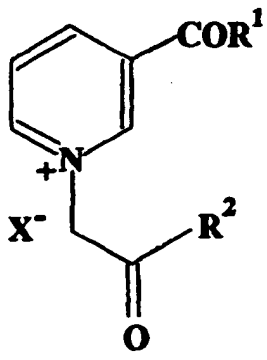
(54) Title: PYRIDINIUM DERIVATIVES FOR THE TREATMENT OF DIABETIC AND AGING-RELATED VASCULAR COMPLICATIONS



(I)

(57) Abstract: The invention discloses compounds of the pyridinium series useful for the management of diabetes and aging-related vascular complications, and particularly in the treatment of complications of diabetes mellitus and other aging-related conditions including kidney disease, nerve damage, atherosclerosis, retinopathy, dermatological conditions and discoloration of teeth by breaking preformed AGE, of general formula (I), or pharmaceutically acceptable salts thereof, wherein, R^1, R^2 and X are as defined in the specification. The invention also discloses method of preparation of the compounds of the series and pharmaceutical composition having one or more compounds as defined above as active ingredients. The invention further discloses a method of treatment of a diabetic patient by administering the compounds as defined above, either singly or in combination with other drugs for antidiabetic therapy.

PYRIDINIUM DERIVATIVES FOR THE TREATMENT OF DIABETIC AND AGING-RELATED VASCULAR COMPLICATIONS

FIELD OF THE INVENTION

The present invention relates to a class of compounds of pyridinium series and to their use in treatment of diabetes and related illnesses. More particularly the invention relates to compounds of this series, methods for their preparation, pharmaceutical composition containing these compounds and their use in the treatment of complications of diabetes mellitus. The compounds of this series exhibit AGE breaking activity, which is essential for the treatment of diabetic and aging-related complications including kidney disease, nerve damage, atherosclerosis, retinopathy and dermatological conditions. The invention also extends to the method of reversing the discoloration of teeth resulting from nonenzymatic browning in the oral cavity which comprises administration of an amount effective to reverse pre-formed advanced glycosylation crosslinks.

BACKGROUND OF THE INVENTION

Maillard in 1912 found that reducing sugars, such as glucose and ribose react with proteins to form brown pigments. Further studies have shown that this is an irreversible non-enzymatic reaction, which occurs in several natural systems including stored foodstuff. Maillard reaction occurs in two stages, early and

advanced. Initially, proteins react with glucose to form stable Amadori products, which subsequently cross-links to form advanced glycation end products (AGE). In most cases, the formation of AGE also accompanies browning of the proteins and increase in the fluorescence.

In diabetes, where blood glucose level is significantly higher than normal, the reaction of glucose with several proteins such as haemoglobin, lens crystallin and collagen, gives rise to the formation of AGE, which in turn, is responsible for the complications associated with diabetes, such as nephropathy, microangiopathy, endothelial dysfunction and other organ dysfunctions. In addition, the activity of several growth factors, such as basic fibroblast growth factor, is also impaired. AGE products, unlike normal proteins in tissue, have a slower rate of turnover and replenishment. It has been reported that AGE products may in fact elicit a complex immunological reaction involving RAGE (Receptor for Advanced Glycation End Products) receptors and activation of several incompletely defined immunological processes. It has been documented that diabetes with evidence of microangiopathy and macroangiopathy also show evidence of oxidative stress, the mechanism of which has not been elucidated.

In vitro AGE formation can be studied in the laboratory by incubating reducing sugars, such as ribose or glucose with bovine serum albumin. AGE formation can be detected by increase in the fluorescence or increased cross

reactivity with anti-AGE antibodies. The increase in fluorescence seems to precede formation of AGE specific antigenic epitopes. This increase in fluorescence is used to monitor the increased AGE formation in vitro (Brownlee M et al, Science 1986; 232:1629-1632). In addition to the increase in the fluorescence, one of the most important features of in vitro AGE formation is the formation of antigenic epitopes that are specific to AGE and not to the native proteins. Therefore, it is possible to raise antibodies against advanced glycation end products of one protein and use them to detect AGE formation in other proteins. This has served as an important analytical tool in AGE research.

Due to the clinical significance of AGE formation, many approaches are being used to diagnose, prevent, or revert AGE formation in the body. The formation of AGE could be inhibited by reacting with an early glycosylation product that results from the original reaction between the target protein and glucose. The inhibition was believed to take place as the reaction between the inhibitor and the early glycosylation product appeared to interrupt the subsequent reaction of the glycosylated protein with additional protein material to form the cross linked late stage product. Compounds like aminoguanidine act to inhibit AGE formation by such mechanism.

The formation of AGE on long-lived proteins is also associated with cross-linking of these proteins. The AGE derived protein cross-links have been shown

to be cleaved by compounds like N- phenacyl thiazolium bromide (PTB), which reacts with and cleaves covalent, AGE derived protein cross links (Vasan et al. Nature 1996; 382: 275-278; US 5,853,703, Date of Patent : Dec. 29, 1998). The mechanism of reducing the AGE content in tissues is expected to take place relatively rapidly, in contrast to aminoguanidine, which acts slowly by its very nature of mechanism of action. This current specification is related to compounds of pyridinium class, which break pre-formed AGE, like PTB, and in some cases even more effectively than PTB.

SUMMARY OF THE INVENTION

The main objective of the present invention is to provide a class of compounds of the pyridinium series which are useful for the management of diabetes and aging-related vascular complications, and particularly in the treatment of complications of diabetes mellitus and other aging-related conditions including kidney disease, nerve damage, atherosclerosis, retinopathy and dermatological conditions. The invention also extends the method to reverse the discoloration of teeth resulting from nonenzymatic browning in the oral cavity which comprises administration of an amount effective to reverse the pre-formed advanced glycosylation crosslinks etc.

Another object of the present invention is to provide compounds of the pyridinium series, which exhibit AGE breaking activities.

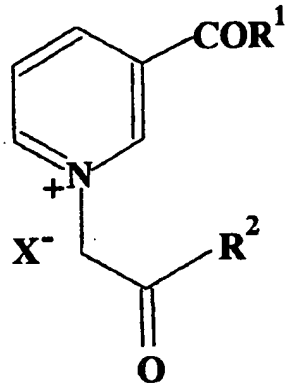
Yet another object of the present invention is to provide a method of preparation of compounds of the pyridinium series which exhibit AGE breaking activities.

Still another object of the invention is to provide pharmaceutical compositions with a new class of compounds of the pyridinium series according to the invention and their pharmaceutically acceptable salts in combination with suitable carriers, solvents, excepients, diluents and other media normally employed in preparing such compositions.

Still another object of the invention is to provide a method of treatment of a diabetic patient by administration of the compounds of the invention, either singly or in combination with drugs for anti-diabetic therapy, or pharmaceutically acceptable salts thereof in required dosage in admixture with pharmaceutically acceptable diluent, solvent, excepients, carriers or other media as may be appropriate for the purpose.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides for a new class of AGE breakers, of general formula I,



(I)

wherein

R^1 is -Y-R^3

Y is selected from oxygen or NH.

R^3 is selected from hydrogen, alkyl, aryl

R^2 is selected from group consisting of alkyl, -Oalkyl, aryl, -Oaryl, -NHalkyl and -NHaryl

X is selected from group consisting of a halide ion, acetate ion, perchlorate ion, sulfonate ion, oxalate ion, citrate ion, tosylate ion, maleate ion, mesylate ion, carbonate ion, sulfite ion, phosphoric hydrogen ion, phosphonate ion, phosphate ion, BF_4^-, PF_6^-, etc.

with proviso that,

(a) when R^1 is phenyl, then R^2 is also phenyl, and

(b) when R^2 is phenyl and X is halide ion, then R^1 is other than -OCH_3.

As used herein "alkyl" refers to an optionally substituted, saturated hydrocarbon group joined by single carbon-carbon bonds and having 1-4 carbon

atoms joined together. The saturated alkyl hydrocarbon group may be linear or branched. The substituent is -OH.

As used herein "aryl" refers to an optionally substituted aromatic group with atleast one ring having a conjugated pi- electron system, containing upto two conjugated or fused ring systems. Aryl includes carbocyclic aryl and heterocyclic aryl all of which may be optionally substituted with halogen, sulfonamido, thio, amino, cyano, -Oalkyl, -NHalkyl, hydroxy, formyl, -Oaryl and -NHaryl.

The representative compounds of general formula I which are novel are listed in Table IA. These compounds with the following chemical names are suggested by way of example alone and in no way restrict the invention.

3-Carbonylamino-1-(2-(2,4-dichlorophenyl)-2-oxoethyl)) pyridinium bromide (compound 1).

3-(Tetrahydrobenzothiazol-2-yl)aminocarbonyl-1-(2-(2,4-dichlorophenyl)-2-oxoethyl)pyridinium bromide (compound 2).

1-(2-Phenyl-2-oxoethyl)-3-((2-hydroxyethyl)aminocarbonyl) pyridinium bromide (compound 3).

3-Carbonylamino-1-(2-thien-2'-yl-2-oxoethyl)pyridinium bromide(compound 4).

1-(2-Phenyl-2-oxoethyl)-3-((p-sulfonamidophenylene)aminocarbonyl) pyridinium bromide (compound 5).

1-(2-Ethoxy-2-oxoethyl)-3-((2-hydroxyethyl)aminocarbonyl)pyridinium bromide. (compound 6).

1-(2-Phenyl -2- oxoethyl) -3-(isopropyloxycarbonyl) pyridinium bromide (compound 7).

1-(2-Methyl-2-oxoethyl)-3-((2-hydroxyethyl)aminocarbonyl) pyridinium chloride (compound 8).

1-(2-Thien-2'-yl-2-oxoethyl)-3-((2-hydroxyethyl)aminocarbonyl)pyridinium bromide (compound 9).

1-(2-(2,4 - Dichlorophenyl-2-oxoethyl) -3- (isopropyloxycarbonyl) pyridinium bromide (compound 10).

1- (2-Phenyl - 2- oxoethyl) - 3- ((4-methylthiazol - 2 -yl) aminocarbonyl) pyridinium bromide (compound 11).

1-(2-Phenylamino-2-oxoethyl)-3-(n-butyloxycarbonyl)pyridinium chloride (compound 12).

1-(2- Phenylamino - 2- oxoethyl) - 3 - (n-butylaminocarbonyl) pyridinium chloride (compound 13).

1- (2- Phenylamino - 2- oxoethyl)- 3- ((2-hydroxyethyl)aminocarbonyl) pyridinium chloride (compound 14).

1- (2- (2,4 - Dichlorophenyl) - 2-oxoethyl) - 3- (n - butoxycarbonyl) pyridinium bromide (compound 15).

1-(2 - (2, 4 - Dichlorophenyl) - 2-oxoethyl) - 3- (n-butylamino-carbonyl) pyridinium bromide (compound 16).

Further, some known pyridine derivatives have also been studied for their AGE breaking activity, which was not known earlier for these molecules, and are as listed in Table IB, with their chemical names as given below:

1- (2-Phenyl-2-oxoethyl) -3- (1-phenyl-1-oxomethyl) pyridinium bromide (compound 17 : (Ref: Chemical Abstracts: 91, P47378Y, (1979))

1- (2 Phenyl - 2-oxoethyl) - 3- (methoxycarbonyl) pyridinium bromide (compound 18 : (Ref: Chemical Abstracts: 91, P47378Y, (1979))

Table IA – Pyridinium derivatives (Novel)

Compound No.	$-R^1$	$-R^2$	-X
1	NH_2	2,4-dichlorophenyl	Br
2	tetrahydrobenzo-thiazol-2-yl-amino	2,4-dichlorophenyl	Br
3	$NHCH_2CH_2OH$	Phenyl	Br
4	NH_2	2-thienyl	Br
5	(p-sulfonamido-phenylene)amino	Phenyl	Br
6	$NHCH_2CH_2OH$	OEt	Br
7	$OCH(CH_3)_2$	Phenyl	Br
8	$NHCH_2CH_2OH$	CH_3	Cl
9	$NHCH_2CH_2OH$	2-thienyl	Br
10	$OCH(CH_3)_2$	2,4-dichlorophenyl	Br
11	(4-methylthiazol-2-yl)amino	Phenyl	Br
12	$OCH_2CH_2CH_2CH_3$	NHPh	Cl
13	$NHCH_2CH_2CH_2CH_3$	NHPh	Cl

14	$NHCH_2CH_2OH$	NHPh	Cl
15	$OCH_2CH_2CH_2CH_3$	2,4-dichlorophenyl	Br
16	$NHCH_2CH_2CH_2CH_3$	2,4-dichlorophenyl	Br

Table IB - Pyridinium Derivatives (Known)

Compound No.	$-R^1$	$-R^2$	-X
17	Phenyl	Phenyl	Br
18	OCH_3	Phenyl	Br

According to one embodiment of the present invention, the present compounds are used for the treatment of diabetic complications, aging-related complications including kidney disease, nerve damage, atherosclerosis, retinopathy, dermatological conditions and colouration of teeth occurring due to the higher levels of preformed AGE. The increased levels of preformed AGE can be brought under control by breaking the AGE products using compounds mentioned in the invention.

The invention also provides a process for the preparation of compounds of the pyridinium series.

The said process for the preparation of compound 1, comprises, adding a solution of 2,4- dichlorophenacyl bromide in toluene to nicotinamide dissolved in refluxing toluene, refluxing for seven and half hours, cooling, filtering the precipitated solid, dissolving in methanol, treating with activated charcoal,

concentrating under vacuum, cooling in ice-salt mixture, filtering the precipitated solid and washing with methanol to obtain the desired compound.

Similarly, the other compounds of general formula I, are prepared from properly substituted pyridine derivatives followed by quarternization with appropriate reagent by refluxing in alcoholic solvents like methanol, ethanol, propanol, etc., and high boiling solvents like, toluene or xylene for 6 - 48 hrs. to give the desired compounds.

The in vitro AGE formation, studied in the laboratory, by incubating reducing sugar ribose, with protein bovine serum albumin, resulted in browning of solution and increase in the fluorescence. Fluorescence was used as the criteria to monitor the increased AGE formation.

Example 1

AGE breaker activity has been confirmed by the screening procedure as mentioned below:

Materials:

Bovine serum albumin (fraction V) (BSA)

Ribose, analytical grade

Phosphate buffered saline (PBS)

Equipment:

Microplate ELISA Reader - Spectramax Plus (Molecular Devices, USA)

Microplate washer, (Bio -Tec Instruments, USA)

pH meter

Methods of experiment:

160 mg/ml of protein, bovine serum albumin, BSA and 1.6M glucose sugar were dissolved in phosphate buffered saline, PBS. Sodium azide was added at 0.02% concentration as a preservative. The solution was filtered asceptically through a 0.22 μM filter and kept for aging at 37°C for 16 weeks. After 16 weeks the solution was dialyzed against PBS, aliquoted and stored at -20°C.

To determine the AGE breaking activity, 10μg/ml and 100μg/ml of the 16 weeks AGE-BSA was incubated with different concentrations of the test compounds at 37°C for 24 hours and AGE breaking activity of the test compounds by ELISA was determined.

ELISA was performed as follows:

1. Different concentrations of 16 weeks AGE-BSA were coated on a microtitre plate as standard. Each concentration is coated in triplicates.

2. The test samples were coated on microtitre plate at a concentration of 5 ng. to 20 ng per well in triplicates.

3. The plate was incubated at 37°C for one hour.

4. After incubation the plate was washed with PBST (PBS with 0.05% Tween 20).

5. Blocking with 5 % skimmed milk in PBS at 37°C for one hour was done.

6. The plate was washed with PBST.

7. Primary antibody against AGE-BSA was added and the plate is incubated at 37°C for one hour.

8. The plate was washed with PBST

9. Secondary antibody anti rabbit HRPO (Horse-Radish Per Oxidase) conjugate was added and the plate is incubated at 37°C for one hour.

10. The plate was washed with PBST.

11. Colour development with OPD (orthophenylenediamine dihydrochloride) and hydrogen peroxide was done.

12. OD (optical density) at (450nm reading - 620nm reading) was measured after incubation at 37°C for 15 minutes with Microplate ELISA Reader.

The breaker activity of the compounds were determined by the following formula:

$$\% \text{ Breaker activity} = \frac{OD_{450\text{-}620}\text{Control} - OD_{450\text{-}620}\text{Test}}{OD_{450\text{-}620}\text{ Control}} \times 100$$

$OD_{450\text{-}620}$Control=Absorbance of 20ng AGE-BSA after incubation at 37°C for 24 hours without test compound

$OD_{450-620}$Test=Absorbance of 20ng AGE-BSA after incubation at 37°C for 24 hours with required concentration of test compound

Using specific examples, the % AGE breaking activity was calculated and recorded in Table 2.

Table 2

Sample	Concentration	%Breakage
PTB	10 mM	27
	20 mM	47
Compound 3	10 mM	5
Compound 4	10 mM	3
Compound 6	10 mM	43
Compound 9	10 mM	50
Compound 12	10 mM	57
Compound 13	10 mM	27
Compound 14	20 mM	48
Compound 17	5 mM	45
Compound 18	20 mM	36

Hence, for example, compound 12 has significant AGE - breaking activity i.e. a comparatively much superior potency vis - a - vis PTB.

The following examples give method for preparation of the specific compounds of the invention as given in Table 1. The following compounds suggested are by way of example alone and in no way restrict the invention.

Example 2

Preparation of 3- carbonylamino -1- (2- (2,4-dichlorophenyl) -2- oxoethyl) pyridinium bromide (compound 1)

Nicotinamide (1.22g, 0.01 mol) was dissolved in refluxing toluene (40 ml) and a solution of 2,4-dichlorophenacyl bromide (3.0g, 0.012mol) in 10ml of toluene was added. The reaction mixture was refluxed for 7.5 hours and cooled. The precipitated solid was filtered and dissolved in methanol, decolourized with activated charcoal and concentrated under vacuum to one-fourth volume. It was cooled in ice - salt mixture and the precipitated solid was filtered and washed with methanol (3x10ml) to afford a pure solid.

Yield : 39%

m.p. : 237-239°C

IR(KBr,cm^{-1}) : 3331, 3133, 1706, 1678

^1H NMR ($DMSOd_6$, 400 MHz) δ : 9.54(1H,s), 9.18-9.11(2H,m), 8.67(1H,s), 8.40(1H,t), 8.42-8.38(2H,m), 7.88(1H,s), 7.75 -7.72(1H,m), 6.49(2H,s)

Mass (m/z): 309,310,311,312,187,159

According to the above mentioned procedure the following compounds are synthesized by reacting the corresponding pyridine derivatives with appropriate reagents by refluxing in alcoholic solvents like methanol, ethanol, propanol, etc. and high boiling solvents like toluene or xylene for 6-48 hours to give the desired compounds:

Example 3

3-(Tetrahydrobenzothiazol-2-yl)aminocarbonyl)-1-(2-(2,4-dichlorophenyl)-2-oxoethyl) pyridinium bromide (compound 2):

Yield : 48%

m.p. : 165 - 167 °C(decomp.)

IR(KBr,cm^{-1}) : 3333, 1714, 1684, 1635

^1H NMR(CD_3OD, 400MHz) δ: 9.45(1H,s), 9.27-9.24(1H,m), 8.92-8.91(1H, m), 8.24 – 8.21(1H, m), 8.01 – 7.99(1H, m), 7.72 – 7.71(1H, m) 7.57-7.54(1H,m), 2.59-2.57 (4H,m), 1.85(4H,m)

Mass (m/z) : 446, 447, 448, 449, 416, 307 and 266

Example 4

1-(2- Phenyl -2- oxoethyl) -3- ((2- hydroxyethyl) aminocarbonyl) pyridinium bromide (compound 3):

Yield : 98%

m.p. : 182 - 184°C(decomp.)

IR(KBr,cm^{-1}) : 3289, 3241, 1690 and 1660

^1H NMR($DMSOd_6$, 400MHz) δ: 9.47(1H,s), 9.21(1H,t), 9.09(2H,t), 8.41-8.37(1H,m), 8.08-8.04(2H,m), 7.82-7.78(1H,m), 7.69-7.65(2H,m), 6.52(2H,s), 4.86(1H,t), 3.58-3.54(2H,m), 3.42-3.38(2H,m)

Mass (m/z) : 285,242,149,119,91

Example 5

3-Carbonylamino-1- (2-thien-2'-yl-2-oxoethyl) pyridinium bromide (compound 4).

Yield : 35%

m.p. : 212 - 215°C (decomp.)

IR(KBr,cm^{-1}) : 3295, 3126, 1680, 1671, 1640

^1H NMR ($DMSOd_6$, 400 MHz) δ: 9.49(1H,s), 9.13-9.11(1H,d), 9.07-9.05(1H,d), 8.60(1H,bs), 8.40-8.38(1H,m), 8.25-8.19(3H,m),7.43-7.40,(1H,t), 6.44(2H,s)

Mass(m/z) : 247,248,249,193

Example 6

1- (2-Phenyl -2- oxoethyl) -3- ((p-sulfonamidophenylene) aminocarbonyl) pyridinium bromide (compound 5):

Yield : 44%

m.p. : 188-190°C

IR(KBr,cm^{-1}) : 3296, 1700, 1679.

^{1}H NMR (DMSOd_6, 400MHz) δ: 11.25 (1H,s), 9.58 (1H,s), 9.25 (1H,d), 9.16 (1H, d), 8.45 (1H,t), 8.10 (2H,d), 7.94 (2H,d), 7.86 (2H,d), 7.82(1H,t), 7.68(2H,t), 7.36(2H,s), 6.5(2H,s)

Mass (m/z) : 396, 277

Example 7

1- (2- Ethoxy -2- oxoethyl) -3- ((2- hydroxyethyl) aminocarbonyl) pyridinium bromide (compound 6):

Yield : 87%

m.p. : 138-140°C

IR(KBr, cm^{-1}) : 1748,1669

^{1}H NMR (CD_3OD, 400 MHz) δ: 9.43 (1H,s), 9.09-9.02 (2H,m), 8.26 (1H,m), 5.64 (2H,s), 4.31 (2H,q), 3.73 (2H,t), 3.54 (2H,t), 1.32 (3H,t)

Mass (m/z) : 251, 252, 165, 166

Example 8

1- (2- Phenyl -2- oxoethyl) -3- (isopropyloxycarbonyl) pyridinium bromide (compound 7):

Yield : 46%

m.p. : 172-174°C

IR(KBr, cm^{-1}) : 1726, 1692

^{1}H NMR (DMSOd_6, 400MHz) δ: 9.55 (1H,s), 9.16 (1H,d), 9.08(1H,d), 8.39-8.36 (1H,m), 8.04 (2H,d), 7.77 (1H,t), 7.64 (2H,t), 6.53 (2H,s), 5.25-5.19 (1H,m), 1.34 (6H,d)

Mass (m/z) : 284, 285, 242

Example 9

1- (2- Methyl-2-oxoethyl) -3- ((2- hydroxyethyl) aminocarbonyl) pyridinium chloride (compound 8):

Yield : 47%

m.p. : 178-180°C

IR(KBr, cm^{-1}) : 1727, 1660

^{1}H NMR (DMSOd_6, 400 MHz) δ: 9.33 (1H,t), 9.30 (1H,s), 9.06(1H,d), 8.90 (1H,d), 8.25-8.21 (1H,m), 5.75 (2H,s), 4.84(1H,bs), 3.47 (2H,t), 3.30 (2H,t), 2.23 (3H,s)

Mass (m/z) : 223, 224, 225

Example 10

1- (2- Thien -2'-yl -2- oxoethyl) -3- ((2- hydroxyethyl) aminocarbonyl) pyridinium bromide (compound 9):

Yield : 60%

m.p. : 207-209°C

IR(KBr, cm^{-1}) : 1673, 1656

^{1}H NMR (DMSOd_6, 400MHz) δ: 9.47 (1H,s), 9.18-9.05 (3H,m),8.38-8.34 (1H,m), 8.23-8.19 (2H,m), 7.39 (1H,t), 6.44 (2H,s),3.55-3.50 (2H,m), 3.40-3.37 (2H,m)

Mass (m/z) : 291, 292, 293

Example 11

1- (2- (2,4- Dichlorophenyl) -2- oxoethyl) -3- (isopropyloxycarbonyl) pyridinium bromide (compound 10):

Yield : 26%

m.p. : 160-162°C

IR (KBr, cm^{-1}) : 1726, 1705

^{1}H NMR (DMSOd_6, 400 MHz) δ: 9.55 (1H,s), 9.15 (1H,d), 9.08(1H,d), 8.40-8.36 (1H,m), 8.11 (1H,d), 7.89 (1H,bs), 7.75-7.72 (1H,m), 6.44 (2H,s), 5.26-5.20 (1H,m), 1.34 (6H,d).

Mass (m/z) : 352, 353, 354, 310

Example 12

1- (2- Phenyl -2- oxoethyl) -3- ((4- methylthiazol -2- yl) aminocarbonyl) pyridinium bromide (compound 11):

Yield : 30%

m.p. : 165-167°C

IR (KBr, cm^{-1}) : 3409, 3319 and 1698

^1H NMR ($DMSOd_6$, 400 MHz) δ: 9.58 (1H,s), 9.22 (1H,d), 9.11(1H,d), 8.42-8.38 (1H,m), 8.07 (2H,d), 7.81 (1H,t), 7.68(2H,t), 6.86 (1H,bs), 6.56 (2H,s), 2.30 (3H,s)

Mass (m/z) : 337, 338, 232, 105.

Example 13

1- (2- Phenylamino -2- oxoethyl) -3- (n- butoxycarbonyl) pyridinium chloride (compound 12):

Yield : 10%

m.p. : 150-152°C

IR (KBr, cm^{-1}) : 3228, 1742, 1678 (bs)

^1H NMR ($DMSOd_6$, 400 MHz) δ: 10.96 (1H,s), 9.65 (1H,s), 9.28(1H,t), 9.09 (1H,d), 8.37 – 8.34 (1H,m), 7.62 – 7.59 (2H,m),7.37 – 7.33 (2H,m), 7.11 (1H,t), 5.79 (2H,s), 4.41(2H,t), 1.76-1.72(2H,m), 1.48-1.43 (2H,m), 0.94 (3H,t)

Mass (m/z) : 314, 315

Example 14

1- (2- Phenylamino -2- oxoethyl) -3- (n- butylaminocarbonyl) pyridinium chloride (compound 13):

Yield : 37%

m.p. : 182-185°C

IR (KBr, cm^{-1}) : 3245, 1742, 1679

^1H NMR ($DMSOd_6$, 400MHz) δ: 10.97 (1H,s), 9.50(1H,s), 9.24(1H,t), 9.13 (1H,d), 9.02 (1H,d), 8.28-8.25 (1H,m), 7.57 (2H,d), 7.30(2H,t), 7.05 (1H,t), 5.70 (2H,s), 3.30 – 3.26 (2H,m), 1.52 – 1.48 (2H,m), 1.34 – 1.30 (2H,m), 0.86 (3H,t)

Mass (m/z) : 312, 313

Example 15

1- (2- Phenylamino -2- oxoethyl) -3- ((2- hydroxyethyl) aminocarbonyl) pyridinium chloride (compound 14):

Yield : 58%

m.p. : 225-227°C

IR (KBr, cm^{-1}) : 3448, 3271, 1702 and 1663

^1H NMR ($DMSOd_6$,400 MHz) δ: 11.07 (1H,s), 9.58 (1H,s) 9.35(1H,t), 9.17 (1H,d), 9.11 (1H,d), 8.33-8.29 (1H,m), 7.60(2H,d), 7.32 (2H,t), 7.08 (1H,t), 5.75 (2H,s), 4.90 (1H,t), 3.57-3.53 (2H,m), 3.40-3.36 (2H,m)

Mass (m/z) : 300, 301, 302

Example 16

1- (2- (2,4- Dichlorophenyl) -2- oxoethyl) -3- (n- butoxycarbonyl) pyridinium bromide (compound 15):

Yield : 38%

m.p. : 154-156°C

IR(KBr, cm^{-1}) : 3435, 3389, 1731 and 1704

^1H NMR ($DMSOd_6$, 400 MHz) δ: 9.60 (1H,s), 9.21 (1H,d), 9.14(1H,d), 8.43 (1H,t), 8.16 (1H,d), 7.92 (1H,s), 7.78-7.76(1H,m), 6.51 (2H,s), 4.42 (2H,t), 1.76-1.72 (2H,m), 1.48-1.42 (2H,m), 0.94 (3H,t)

Mass (m/z) : 366, 367, 368, 369, 370

Example 17

1- (2- (2,4- Dichlorophenyl) -2- oxoethyl) -3- (n-butylaminocarbonyl) pyridinium bromide (compound 16):

Yield : 35%

m.p. : 142-144°C

IR(KBr, cm^{-1}) : 3382, 1698, 1672

^1H NMR ($DMSOd_6$, 400 MHz) δ: 9.37 (1H,s), 9.07 (1H,t), 8.99(2H,t), 8.31-8.28 (1H,m), 8.04 (1H,d) 7.82-7.81 (1H,d), 7.68-7.65 (1H,m), 6.34(2H,s), 3.27-3.24 (2H,m), 1.47-1.43 (2H,m),1.29-1.24 (2H,m), 0.81 (3H,t)

Mass (m/z) : 365, 366, 367, 368, 369

Pharmaceutical Compositions

Pharmaceutical compositions may be prepared with a pharmaceutically effective quantity of compounds of general formula I, individually or in combination. The following pharmaceutical formulations suggested are by way of example alone and in no way restrict the forms in which they can be used.

Oral formulations

Oral formulations may be administered as solid dosage forms for example pellets, powders, sachets or discreet units such as tablets or capsules and like. Other orally administered pharmaceutical preparations include monophasic and biphasic liquid dosage forms either in ready to use form or forms suitable for reconstitution such as mixtures, syrups, suspensions or emulsions. The preparations in addition may contain diluents, dispersing agents, buffers, stabilizers, solubilizers, surfactants, preservatives, chelating agents and/ or other pharmaceutical additives as are used. Aqueous or non-aqueous vehicle or their combination may be used and if desired may contain suitable sweetener, flavoring agent or similar substances. In case of suspension or emulsion a suitable thickening agent or suspending agent or emulsifying agent may be present in addition. Alternatively, the compounds may be administered as such in their pure form unassociated with other additives for example as capsules or sachets. It may also be administered with a vehicle. Pharmaceutical preparations can have a slow, delayed or controlled release of active ingredients as is provided by a matrix or diffusion controlled system.

When the present invention or its salts or suitable complexes is presented as a discreet unit dosage form like a tablet, it may contain in addition medically inert excipients as are used in the art. Diluents such as starch, lactose, dicalcium

phosphate, talc, magnesium stearate, polymeric substances like methyl cellulose, fatty acids and derivatives, sodium starch glycollate, etc. may also be used.

Example 18

Preparation of oral dosage form:

A typical tablet has the following composition:

Active ingredient of formula I	as given above
Lactose	135 mg
Starch	76 mg
Polyvinyl pyrolidone (K-30)	2 mg
Talc	1.5 mg
Magnesium Stearate	1.0 mg

Parenteral Formulations

For parenteral administration, the compounds or their salts or suitable complexes thereof may be present in a sterile vehicle which may be an aqueous or non aqueous vehicle or a combination thereof. The examples of vehicles are water, ethyl oleate, oils and derivatives of polyols, glycols and their derivatives. It may contain additives common in injectable preparations like stabilizers, solubilizers, pH modifiers, buffers, antioxidants, cosolvents, complexing agents, tonicity modifiers, etc.

Some suitable additives are for example tartrate, citrate or similar buffers, alcohol, sodium chloride, dextrose and high molecular weight polymers. Another alternative is sterile powder reconstitution. The compound may be administered in the form of injection for more than once daily administration, or intravenous infusion/ drip or suitable depot preparation.

Example 19

Preparation suitable for parenteral administration has the following composition:

Active ingredient of formula I	as given above
Polyethylene glycol (400)	0.75 ml
Sodium metabisulphite	0.01%
Isotonic saline/ WFI	q.s.

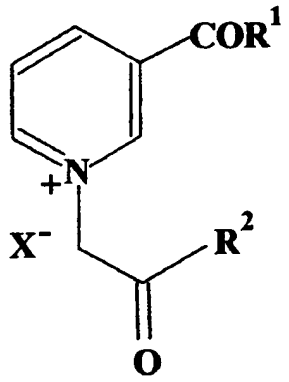
Other Formulations.

For the dermatological application and for the discoloration of teeth, the recommended formulations are lotions, oral rinse and toothpaste containing appropriate amount of the compounds of general formula I.

The above examples are presented by way of illustration alone and in no way limit the scope of the invention.

I CLAIM :

1. A compound of pyridinium series of general formula I and its pharmaceutically acceptable salts, useful for the management of vascular complications associated with diabetes and aging-related disorders,



(I)

wherein

R^1 is -Y-R^3

Y is selected from oxygen or NH.

R^3 is selected from hydrogen, alkyl, aryl

R^2 is selected from group consisting of alkyl, -Oalkyl, aryl, -Oaryl, -NHalkyl and -NHaryl

X is selected from group consisting of a halide ion, acetate ion, perchlorate ion,

sulfonate ion, oxalate ion, citrate ion, tosylate ion, maleate ion, mesylate ion, carbonate ion, sulfite ion, phosphoric hydrogen ion, phosphonate ion, phosphate ion, BF_4^-, PF_6^-,

with proviso that,

(a) when R^1 is phenyl then R^2 is also phenyl, and

(b) when R^2 is phenyl and X is a halide ion, R^1 is other than $-OCH_3$.

2. The compound as claimed in claim 1, wherein X is a halide ion.

3. The compound as claimed in claim 1, which is selected from the group consisting of the following compounds :

a) 1-(2-phenylamino-2-oxoethyl)-3-(n-butyloxycarbonyl) pyridinium chloride or a pharmaceutically acceptable salt thereof.

b) 1-(2-thien-2'-yl-2-oxoethyl)-3-((2-hydroxyethyl) aminocarbonyl)pyridinium bromide or a pharmaceutically acceptable salt thereof.

c) 1-(2-ethoxy-2-oxoethyl)-3-((2-hydroxyethyl) aminocarbonyl) pyridinium bromide or a pharmaceutically acceptable salt thereof.

d) 1-(2-phenylamino-2-oxoethyl)-3-(n-butylaminocarbonyl) pyridinium chloride or a pharmaceutically acceptable salt thereof.

e)1-(2-phenylamino-2-oxoethyl)-3-((2-hydroxyethyl) aminocarbonyl)pyridinium chloride or a pharmaceutically acceptable salt thereof.

f) 1-(2-phenyl-2-oxoethyl)-3-((2-hydroxyethyl) aminocarbonyl)pyridinium

bromide or a pharmaceutically acceptable salt thereof.

g) 1-(2-methyl-2-oxoethyl)-3-((2-hydroxyethyl) aminocarbonyl)pyridinium bromide or a pharmaceutically acceptable salt thereof.

h) 1-(2-phenyl-2-oxoethyl)-3-((4-methylthiazol-2-yl) aminocarbonyl)pyridinium bromide or a pharmaceutically acceptable salt thereof.

i) 1-(2-(2,4-dichlorophenyl-2-oxoethyl)-3-(isopropyloxycarbonyl)pyridinium bromide or a pharmaceutically acceptable salt thereof.

j) 3-(tetrahydrobenzothiazol-2-yl)aminocarbonyl)-1-(2-(2,4-dichlorophenyl)-2-oxoethyl)pyridinium bromide or a pharmaceutically acceptable salt thereof.

k)1-(2-phenyl-2-oxoethyl)-3-((p-sulfonamidophenylene)aminocarbonyl)) pyridinium bromide or a pharmaceutically acceptable salt thereof.

l)3-carbonylamino-1-(2-thien-2'-yl-2-oxoethyl)pyridinium bromide or a pharmaceutically acceptable salt thereof.

m) 1-(2-(2,4-dichlorophenyl)-2-oxoethyl)-3-(n-butylaminocarbonyl)pyridinium bromide or a pharmaceutically acceptable salt thereof.

n) 1-(2-(2,4-dichlorophenyl)-2-oxoethyl)-3-(n-butoxycarbonyl)pyridinium bromide or a pharmaceutically acceptable salt thereof.

4. A process for the preparation of compounds of the pyridinium series as claimed in claim 1, wherein said process comprises preparation of the properly substituted pyridine derivatives according to the desired end products followed

by quaternization of the substituted pyridine derivatives with appropriate reagent by refluxing in alcoholic solvents and/or high boiling solvents for 6 to 48 hrs. to give the desired compounds.

5. The use of a compound of general formula I as defined in claim 1, in the manufacture of a medicament for diabetic complications and aging-related diseases, including kidney disease, nerve damage, retinopathy, atherosclerosis, microangiopathy, endothelial dysfunctions, dermatological conditions, discoloration of teeth and other organ dysfunctions.

6. The use as claimed in claim 5, wherein said compound is selected from the group consisting of :

a) 1-(2-phenylamino-2-oxoethyl)-3-(n-butyloxycarbonyl) pyridinium chloride or a pharmaceutically acceptable salt thereof.

b) 1-(2-thien-2'-yl-2-oxoethyl)-3-((2-hydroxyethyl) aminocarbonyl)pyridinium bromide or a pharmaceutically acceptable salt thereof.

c) 1-(2-ethoxy-2-oxoethyl)-3-((2-hydroxyethyl) aminocarbonyl)pyridinium bromide or a pharmaceutically acceptable salt thereof.

d) 1-(2-phenylamino-2-oxoethyl)-3-(n-butylaminocarbonyl) pyridinium chloride or a pharmaceutically acceptable salt thereof.

e) 1-(2-phenylamino-2-oxoethyl)-3-((2-hydroxyethyl)aminocarbonyl) pyridinium chloride or a pharmaceutically acceptable salt thereof.

f) 1-(2-phenyl-2-oxoethyl)-3-((2-hydroxyethyl) aminocarbonyl)pyridinium bromide or a pharmaceutically acceptable salt thereof.

g) 1-(2-methyl-2-oxoethyl)-3-((2-hydroxyethyl) aminocarbonyl)pyridinium bromide or a pharmaceutically acceptable salt thereof.

h) 1-(2-phenyl-2-oxoethyl)-3-((4-methylthiazol-2-yl) aminocarbonyl)pyridinium bromide or a pharmaceutically acceptable salt thereof.

i) 1-(2-(2,4-dichlorophenyl-2-oxoethyl)-3-(isopropyloxycarbonyl)pyridinium bromide or a pharmaceutically acceptable salt thereof.

j) 3-(tetrahydrobenzothiazol-2-yl)aminocarbonyl-1-(2-(2,4-dichlorophenyl)-2-oxoethyl)pyridinium bromide or a pharmaceutically acceptable salt thereof.

k)1-(2-phenyl-2-oxoethyl)-3-((p-sulfonamidophenylene)aminocarbonyl) pyridinium bromide or a pharmaceutically acceptable salt thereof.

l) 3-carbonylamino-1-(2-thien-2'-yl-2-oxoethyl)pyridinium bromide or a pharmaceutically acceptable salt thereof.

m) 1-(2-(2,4-dichlorophenyl)-2-oxoethyl)-3-(n-butylaminocarbonyl)pyridinium bromide or a pharmaceutically acceptable salt thereof.

n) 1-(2-(2,4-dichlorophenyl)-2-oxoethyl)-3-(n-butoxy carbonyl)pyridinium bromide or a pharmaceutically acceptable salt thereof.

7. The use of 1-(2-phenyl-2-oxoethyl)-3-(1-phenyl-1-oxomethyl)pyridinium bromide or a pharmaceutically acceptable salt thereof in the manufacture of a

medicament for diabetic complications and ageing related diseases including kidney disease, nerve damage, retinopathy, atherosclerosis, microangiopathy, endothelial dysfunctions, dermatological conditions, discoloration of teeth and other organ dysfunctions.

8. The use of 1-(2-phenyl-2-oxoethyl)-3-(methoxycarbonyl) pyridinium bromide or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for diabetic complications and ageing related diseases including kidney disease, nerve damage, retinopathy, atherosclerosis, microangiopathy, endothelial dysfunctions, dermatological conditions, discoloration of teeth and other organ dysfunctions.

9. A pharmaceutical composition for treatment of diabetic complications and aging related diseases which comprises a pharmaceutically effective amount of one or more compounds of general formula I ,as defined in claim 1, or pharmaceutically acceptable salt(s) thereof, in admixture with a pharmaceutically acceptable carrier, diluent, solvent or excepient.

10. The pharmaceutical composition as claimed in claim 9, in the form of an oral formulation.

11. The pharmaceutical composition as claimed in claim 10, wherein the said

pharmaceutically acceptable carrier is selected from one or more of the compounds starch, lactose, polyvinylpyrolidone (K-30), talc and magnesium stearate.

12. The pharmaceutical composition as claimed in claim 9, in the form of parenteral formulation.

13. A method for the preparation of a parenteral formulation as claimed in claim 12, which comprises dissolving the active ingredient of general formula I, as defined in claim 1, in polyethylene glycol 400 and diluting the solution so obtained, with an isotonic solution or water to the desired concentration.

14. The pharmaceutical composition as claimed in claim 9, in the form of lotions, oral rinse and toothpaste.

15. A method for treating a diabetic patient by breaking the preformed AGE within said patient, which comprises administering an effective amount of a compound as claimed in claim 1, either singly or in combination with other drugs for antidiabetic therapy.

16. A method for treating a diabetic patient by breaking the preformed AGE within said patient which comprises, administering an effective amount of 1-(2-phenyl-2-oxoethyl)-3-(1-phenyl-1-oxomethyl)pyridinium bromide or a pharmaceutically acceptable salt thereof, either singly or in combination with other drugs for antidiabetic therapy.

17. A method for treating a diabetic patient by breaking the preformed AGE, within said patient, which comprises, administering an effective amount of 1-(2-phenyl-2-oxoethyl)-3-(methoxycarbonyl)pyridinium bromide or a pharmaceutically acceptable salt thereof ,either singly or in combination with other drugs for antidiabetic therapy.

18. A method of preventing or treating diseases caused by diabetes and aging-related complications, which comprises, administering to a patient in need thereof ,an effective amount of a compound of formula I, as claimed in claim 1, either singly or in combination with a pharmaceutically acceptable carrier, diluent or excepient.

19. The method as claimed in claim 18, wherein the disease caused to be prevented or treated is a nephrological disorder, neurological disorder, atherosclerosis, retinal disorder, dermatological disorder, non-enzymatic browning of oral cavity, endothelial or other organ dysfunction and growth impairment.

INTERNATIONAL SEARCH REPORT

Im ational Application No
PCT/IB 99/01687

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D213/82 C07D417/12 C07D409/06 A61K31/4427 A61K31/4425
A61P37/00 A61P3/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 853 703 A (EGAN JOHN J ET AL) 29 December 1998 (1998-12-29) cited in the application column 32 -column 34; claim 1 -/--	1,5,7-19

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 March 2000	17/04/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Bosma, P

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int. tional Application No
PCT/IB 99/01687

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 91, no. 6, 6 August 1979 (1979-08-06) Columbus, Ohio, US; abstract no. 47378, TABUCHI, KATSUHIKO ET AL: "Electrochromic display devices" page 534; XP002134411 cited in the application abstract -& DATABASE CAPLUS 'Online! XP002134414 see CAS RN 5469-10-3 and 16844-14-7 & JP 53 131289 A (TDK ELECTRONICS CO., LTD., JAPAN) 15 November 1978 (1978-11-15) ---	1,2
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X	EP 0 356 152 A (HAMARI YAKUHIN KOGYO KK) 28 February 1990 (1990-02-28) example 6 ---	1,2,9
X	DD 275 872 A (UNIV DRESDEN TECH) 7 February 1990 (1990-02-07) see formula III ---	1,2
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X	US 3 823 076 A (RUSHMERE J) 9 July 1974 (1974-07-09) see compound 5 claim 1 ---	1,2
X	FR 1 427 282 A (THE UDYLITE CORPORATION) 20 April 1966 (1966-04-20) see compounds 20, 32-34, 37 ---	1,2
X	GB 822 351 A (CILAG LIMITED) 21 October 1959 (1959-10-21) the whole document ---	1,2
	-/--	

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INTERNATIONAL SEARCH REPORT

Int. tional Application No
PCT/IB 99/01687

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	FUJII, TOZO ET AL: "Lactams. XI. Construction of the lactam carbonyl function in 1,3-disubstituted piperidines by mercuric acetate-EDTA oxidation: effect of carbonyl and related groups at the 3-position" CHEMICAL AND PHARMACEUTICAL BULLETIN., vol. 25, no. 11, 1977, pages 3042-3048, XP002134408 PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO., JP ISSN: 0009-2363 see compound 2 ---	1,2
X	C. T. BAHNER AND H. KINDER: "3,4-Dihydroxyphenacyl Chloride Quaternary salts of Heterocyclic Nitrogen Compounds" JOURNAL OF ORGANIC CHEMISTRY., vol. 27, 1962, pages 1464-1465, XP002134409 AMERICAN CHEMICAL SOCIETY. EASTON., US ISSN: 0022-3263 see Table 1: bases nicotinic acid ---	1,2
X	C. T. BAHNER ET AL.: "p-Fluorophenacyl Bromide salts" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 74, 1952, page 3960 XP002134410 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC., US ISSN: 0002-7863 see Table I ---	1,2
X	CHEMICAL ABSTRACTS, vol. 54, no. 5, 10 March 1960 (1960-03-10) Columbus, Ohio, US; K. WALLENFELS ET AL.: "The mechanism of hydrogen transfer with pyridine nucleotides." column 4568d; XP002134413 abstract -& DATABASE CAOLD 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US CA 54:4568d , XP002134415 see CAS RN 108749-69-5 and 109962-90-5 --- -/--	1,2

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INTERNATIONAL SEARCH REPORT

Int .tional Application No
PCT/IB 99/01687

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US ARIF, MUHAMMED ET AL: "Synthesis of some phenacyl nicotinates as potential anticholesteremic agents" retrieved from STN Database accession no. 114:228611 XP002134416 see abstract; CAS RN 133432-85-6 and 133432-86-7 & PAK. J. PHARM. SCI. (1990), 3(2), 63-7 ,	1,2
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US F. TOZO ET AL.: "Antitumor activities of some seventy compounds related to lactams and pyridones" retrieved from STN Database accession no. 87:127019 XP002134417 see abstract; CAS RN 59052-34-5 & YAKUGAKU ZASSHI, vol. 97, no. 6, 1977, pages 685-689,	1,2,9
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US J. SHASHI ET AL.: "Synthesis of possible hypoglycemic compounds" retrieved from STN Database accession no. 124:201973 XP002134418 see abstract; CAS RN 174415-72-6 & INDIAN DRUGS, vol. 32, no. 7, 1995, pages 317-319,	1,2,9

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 99/01687

Box I Observations wher certain claims were found uns archabl (Continuation of item 1 of first sh t)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 15 to 19
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 15 to 19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/IB 99 01687

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search has been restricted to the compounds with the meanings of alkyl and aryl radicals as given in the description.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ional Application No
PCT/IB 99/01687

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